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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,197	12/23/2004	Naoto Osakada	00005.001252	3639
5514 7590 08/31/2007 FITZPATRICK CELLA HARPER & SCINTO 30 ROCKEFELLER PLAZA NEW YORK, NY 10112			EXAMINER SEAMAN, D MARGARET M	
			ART UNIT 1625	PAPER NUMBER
			MAIL DATE 08/31/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/519,197

Applicant(s)

OSAKADA ET AL.

Examiner

D. Margaret Seaman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11 and 15-33 is/are rejected.
- 7) ☒ Claim(s) 12-14 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f):
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. ____                                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____   | 6) <input type="checkbox"/> Other: ____                           |

### DETAILED ACTION

This application was filed 12/23/2004 and is a 371 of PCT/JP03/08079 (6/26/2003) which claims priority to JP 2002-185707 (6/26/2002). Claims 1-33 are before the Examiner.

#### *Claim Rejections - 35 USC § 101*

1. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 22-27 and 32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. "Use of" is not statutory subject matter.

#### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 20 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is not seen where the instant specification provides written description for PDE 10a inhibitors outside of formula I or IA. There is no description other than for formulas I and IA or compounds of the prior art known to have certain properties. However, without guidance, written description is lacking.

5. Claims 17-20, 28-31 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not adequately describe the nexus between the inhibition of the PDE 10a receptor and a useful treatment of a disease/condition. There are no working examples of the instantly claimed compounds or of compounds having this PDE10a activity treating or preventing any disease, or specifically treating or preventing dyskinesia or tumor growth. It is not seen where the instant specification adequately describes the nexus between the inhibition of the PDE 10a receptor and a useful treatment or prevention of a single disease or condition.

1. Claims 17-20, 28-31 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

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matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims,
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

**The nature of the invention:** The nature of the invention is the method of treating a disorder that is inhibition of the PDE 10a receptor.

**The state of the prior art:** The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological

activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The predictability in the art:** It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects of all diseases, whether or not the inhibition of the PDE 10a receptors would make a difference in the disease. Hence, in the absence of a showing of a nexus between any and all known diseases and the inhibition of the PDE 10a receptors, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of inhibition of the PDE 10a receptors. Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of

in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, although drawn specifically to cancer cells, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot

duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

**The presence or absence of working examples:** The instant specification does not contain any working examples of the instant compounds treating or preventing any disease or tumors. In the specification, the compounds of formula (I) inhibits hyperkinesias in 6-OHDA-treated rats and therefore, it is considered that the PDE10a inhibitors can reduce dyskinesia. However, this link between hyperkinesias in special rats and the treatment and prevention of dyskinesia has not been shown by working examples.

**The amount of direction or guidance present:** The guidance present in the specification is that of the inhibition of the PDE 10a is useful for treating and/or preventing various diseases caused by enhancing the activity of PDE10A. Among these diseases is dyskinesia and tumors. The instant specification teaches that cyclic nucleotides have been known to mediate cell responses to various extracellular stimuli and Phosphodiesterase (PDE) plays an important role in this intracellular concentration of these cyclic nucleotides. Various subtypes of PDE have been found to number into 11 families. Due to this involvement, PDE10A appears to be involved at the onset or during the progression of diseases related to the cells, tissues and organs. Due to this, the specification teaches that it is expected that an inhibitor having selectivity of PDE10A could be useful for treating and/or preventing various diseases caused by enhancing the activity of PDE10A.



**The breadth of the claims:** Claims 20 and 33 are drawn to treating and/or preventing dyskinesia using any compound, known or unknown, that has PDE10A inhibitory activity. All other claims are drawn to the treatment or prevention of a disease that is caused by enhancing the activity of PDE10A with a compound of formula (I).

**The quantity of experimentation needed:** The quantity of experimentation needed is undue. One skilled in the art would need to determine what diseases out of all known diseases would be benefited by PDE10A inhibitory activity and then would further need to determine which of the claimed compounds of formula (I) would provide treatment of the disease. For claims 20 and 33, one skilled in the art would need to determine if dyskinesia would be benefited by PDE10A inhibitory activity and then would further need to determine what compound(s) or all known and unknown compounds have this activity, and then determine if this activity would benefit dyskinesia. This is undue.

**The level of the skill in the art:** The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of claim 1 for the treatment of any disease. As a result necessitating one of

ordinary skill to perform an exhaustive search for which diseases can be treated by which compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compounds of the instant claims, with no assurance of success.

This rejection can be overcome by deleting the claims.

### *Claim Rejections - 35 USC § 102*

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

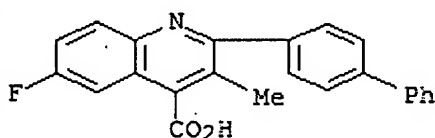
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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3. Claims 1-11, 15-21, 28-31 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Pospisil (abstract only, full document is on order). Pospisil teaches

RN 96187-27-8 CA

CN 4-Quinolinedicarboxylic acid, 2-[1,1'-biphenyl]-4-yl-6-fluoro-3-methyl-  
INDEX NAME)



a

s an PDE inhibitor.

4. Claims 20 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by WO95/17904 which teaches the treatment of tardive dyskinesia with butolinum toxins (see abstract).

5. Claims 1, 3, 20, 28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 2001/77110 and Gomez-Parra. WO and Gomez-Parra both teach 4-methylquinoline as a PDE inhibitor.

### *Claim Objections*

6. Claims 12-14 are objected to as being dependent from a rejected base claim.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. Margaret Seaman whose telephone number is 571-272-0694. The examiner can normally be reached on 730am-4pm, Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



D. Margaret Seaman  
Primary Examiner  
Art Unit 1625

dms